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(54) **Sustained release with high and low viscosity HPMC.**

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CHEMICAL ABSTRACTS, vol. 111, no. 16, 16th october 1989, page 393, abstract no.140370f, Columbus, Ohio, US; G. GEISSLINGER et al.: "Therapeutically relevant differences in the pharmacokinetic and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid", & INT. J.CLIN. PHARMACOL., THER. TOXICOL 1989, 27(7), 324-8

(73) Proprietor: **MERCK & CO. INC.**
126, East Lincoln Avenue
P.O. Box 2000
Rahway
New Jersey 07065-0900 (US)

(72) Inventor: **Lui, Chung Yuen**
423 Shoemaker Way
Lansdale,
PA 19446 (US)

(74) Representative: **Thompson, John Dr. et al**
Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow, Essex CM20 2QR (GB)

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Description

BACKGROUND OF THE INVENTION

Sustained release formulations containing a pharmacologically active agent and exhibiting a zero order release rate are particularly useful.

Ibuprofen is a well-known analgesic which has been used to treat chronic pain such as that associated with arthritic and rheumatic conditions. In such cases the analgesic is best administered so as to sustain its action over a period of time and to have a uniform level of analgesic action over this extended time period. This objective can partly be achieved by the repeated administration of a rapid release dosage. However, this procedure clearly has patient acceptability problems as well as a repeated raising and lowering of the blood levels of analgesic.

Generally, the release profiles in controlled release formulations follow a classical square root of time relationship, i.e., the release rate decreases with time. In a zero order composition a plot of the rate of release of drug vs. time shows a straight horizontal line, i.e., the release rate is independent of time. Zero order sustained release compositions provide a more uniform delivery of the therapeutic agent over long periods of time.

Sustained release formulations for ibuprofen have been disclosed in EP publication 255,404, however the formulations disclosed do not provide for a zero order release rate. In WO 87/00044 a sustained release formulation, exhibiting a bimodal controlled release, is disclosed. The carrier base is composed of a bimodal hydroxypropylmethylcellulose (HPMC) and the medicament selected from an antiflammatory group such as flurbiprofen. The publication is silent on the formulation of zero order release compositions. The Boots Company PLC, EP 234,670 has disclosed a sustained release composition containing xanthan gum wherein the medicament may be ibuprofen. The Boots formulation does not solve the problem of a zero order release rate.

In FR-A-25555901 a controlled long acting dry pharmaceutical formulation comprised of at least three components selected from (a) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose; (b) 0.25 - 4.5% by weight of hydroxy components selected from (1) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose or (2) 0.25 - 4.5% by weight of hydroxypropyl cellulose; and (c) 1-90% by weight of a carboxyvinyl polymer.

This reference discloses that it is the combination of these 3 elements which is critical to the disclosed invention and it does not disclose that varying the ratio of the high density HPMC to the low density HPMC will affect the delivery characteristics of the system but rather suggests that varying the relative amount of the hydroxypropyl methyl cellulose and hydroxypropyl cellulose and carboxyvinyl polymer elements will affect the delivery rate. Nowhere does this reference disclose a mixture comprising a HPMC having a molecular weight of 60,000 or greater together with a HPMC having a molecular weight of 50,000 or less. US-A-4389393 discloses a sustained release rate formulation wherein the ratio between high molecular weight HPMC and low molecular weight HPMC is 45.5:19.5 or 1:0.4. Furthermore, the formulation of this reference shows a significant % drop of released medicant after only 8 hours. US-A-4259314 discloses a method of producing a controlled long acting pharmaceutical composition wherein hydroxypropyl cellulose is considered an essential ingredient. In fact, the reference specifically discloses that the inadequacy of hydroxypropyl methylcellulose for use in long lasting troches is known. WO-A-8700044 discloses non-zero order formulations which can be achieved only by using the disclosed highly unusual biomodal HPMCs (B-HPMCs). US-A-4871548 discloses particular combinations comprising a "low number average molecular weight hydroxypropy methyl cellulose ether" having an average molecular weight of from about 9,000 to 30,000 and viscosities ranging from 3-106 and a "high number average molecular weight hydroxypropyl methyl cellulose" having an average molecular weight of 30,000 to 350,000 and viscosities ranging from 1,500 to 220,000. The ratio of the high and low molecular weight MPCs disclosed in the formulations of this reference is 1:1. Furthermore, these formulations employ an additional ingredient - lactose.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a carrier base material for therapeutically active medicaments in a solid dosage formulation wherein
the carrier base comprises:

a) a high viscosity HPMC; and

b) a low viscosity HPMC wherein the high and low viscosity HPMC are in a ratio yielding a zero order release profile for the medicament.

In the present invention it has unexpectedly been found that a zero-order release profile can be obtained by controlling the ratio of high to low viscosity HPMC in a carrier base formulation.

A high viscosity HPMC is defined as one having a molecular weight of 60,000 or greater. A low viscosity HPMC is defined as one having a molecular weight of 50,000 or less.

The preferred low viscosity HPMCs available as Dow Methocel cellulose ethers, are: E5, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4-6 cP; E15LV, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 12-18 cP; E50LV, 28-30% methoxy, 7-12% hydroxylpropyl, viscosity = 40-60; and K100LV, 19-24% methoxy 7-12% hydroxypropyl, viscosity = 100 cP. The preferred high viscosity HPMCs, available as Dow Methocel cellulose ethers are: E4M-CR, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; E10M-CR, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 10,000 cP; K4M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; K15M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 15,000 cP; and K100M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 100,000 cP.

The medicament in the present invention may be selected from ibuprofen, or salts of ibuprofen. Most preferably the medicament is ibuprofen lysine which should be taken to mean all stereoisomeric configurations including racemic ibuprofen lysine and (S)-ibuprofen-(S)-lysine;i.e. the salt formed from (S)-ibuprofen and (S)-lysine.

It should be appreciated that a zero order release profile is obtained only with a certain relative range of high to low viscosity HPMC. This may be illustrated by the combination of 1 part high viscosity E10M CR and a varying amount of any of the preferred low viscosity HPMC wherein a zero order release was found, for example:

(i) 1 part E10M CR: 3 parts E5;
(ii) 1 part E10M CR: 2 to 4 parts E15LV;
(iii) 1 part E10M CR: 3 to 9 parts E5OLV;
(iv) 1 part E10M CR: 3 to 9 parts K100LV.

These ranges are not limited to combinations where the high viscosity HPMC is E10M CR but are to be expected with any of the other preferred high viscosity HPMC.

The medicament, preferably ibuprofen lysine is mixed with Povidone USP (PVP) which functions as a binding agent. Typically the ratio of drug to PVP is 20:1.

The percent of drug/PVP granules in the pharmaceutical composition is 33.3 to 83%.

The range of ibuprofen in this invention is preferably 100 to 600 mg per tablet.

Where the medicament is ibuprofen lysine the weight range is 100 to 600 mg measured in mg ibuprofen.

The percent range of HPMC carrier base is 17-66%.

An example of the composition and processing of the controlled release dosage form is provided below:

Composition:

Ibuprofen Lysine	61.8%
PVP	3.0%
Carrier Base	34.1%
Magnesium Stearate	1.0%
	Total 99.9%

Fillers such as Avicel, lactose, manitol, dicalcium phosphate, starch or pregelatin starch 1500 may be added to the composition. Binders such as corn starch, pregelatin starch 1500, Klucel LF, methocel E3, E5, gelatin or acacia may be added as necessary by those skilled in the art. Besides magnesium stearate, other lubricants such as stearic acid, sodium stearate fumerate or calcium stearate may be employed.

Processing

A batch of ibuprofen lysine granules containing PVP was prepared. An appropriate amount of granules, typically 3.21 grams was removed and mixed in a V-blender for 10 minutes with a carrier base, usually 1.71 grams, chosen from the preferred high viscosity and low viscosity HPMC. The resultant mixture was then mixed in a V-blender for three minutes with magnesium stearate, which had previously been sieved through a #60 mesh screen. Tablets of about 980 mg were compressed on an F-press.

Tables I-V provide release profiles for controlled release tablets prepared following the processing described above and containing 600 mg Ibuprofen Lysine and 330 mg carrier base. Dissolution determinations were conducted using an automated dissolution testing unit such as a Beckman Spectrophotometer, model DU65, connected with a Vanderkamp 600 six-spindle dissolution tester. Samples were taken every hour for at least 12 to 24 hours and absorbance was read spectrophotometrically at 260 nm.

All the HPMC polymers described are available from the Dow Chemical Company. Racemic ibuprofen lysine may be prepared following the description in U.S. Patent 4,279,926. (S)-ibuprofen-(S)-lysine is prepared as described in copending application S.N. 422,466 filed October 18, 1989.

TABLE I

Release Profiles of Ibuprofen Lysine Using 25% E4MCR and 75% of a Low Viscosity HPMC			
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE	75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000
1	0.1125	0.1160	0.0820
2	0.1885	0.1935	0.1400
3	0.2570	0.2615	0.1940
4	0.3180	0.3230	0.2440
5	0.3735	0.4080	0.2920
6	0.4265	0.5290	0.3375
7	0.4945	0.6265	0.3860
8	0.5975	0.6820	0.4445
9	0.6855	0.7190	0.5045
10	0.7280	0.7405	0.5750
11	0.7520	0.7555	0.6350
12	0.7540	0.7620	0.6845
13	0.7500	0.7675	0.7225
14	0.7445	0.7680	0.7515
15	0.7405	0.7670	0.7695
16			0.7785
17			0.7825
18			0.7835
19			
20			
21			
22			
23			
24			

TABLE II

Release Profiles of Ibuprofen Lysine Using Various Ratios of E10MCR and a Low Viscosity HPMC

Time [hr]	25% E10MCR: 75% E5 MEAN ABSORBANCE	33.3% E10MCR: 66.7% E15LV MEAN ABSORBANCE	20% E10MCR: 80% E15LV MEAN ABSORBANCE
0	0.0000	0.0010	0.0010
1	0.0985	0.1140	0.1615
2	0.1670	0.1720	0.2420
3	0.2335	0.2210	0.3130
4	0.3055	0.2630	0.3760
5	0.3960	0.3050	0.4345
6	0.4800	0.3450	0.5265
7	0.5630	0.3840	0.5975
8	0.6505	0.4220	0.6525
9	0.6875	0.4600	0.7095
10	0.7165	0.4970	0.7475
11	0.7235	0.5345	0.7565
12	0.7255	0.5835	0.7590
13	0.7260	0.6410	0.7600
14	0.7245	0.6915	0.7575
15	0.7240	0.7230	0.7530
16	0.7240	0.7395	0.7525
17	0.7240	0.7425	0.7520
18	0.7245	0.7435	0.7520
19	0.7255	0.7455	
20	0.7265	0.7440	
21	0.7275	0.7420	
22	0.7290	0.7420	
23	0.7290	0.7410	
24	0.7310	0.7395	

TABLE II Cont'd

Time [hr]	25% E10MCR 75% E50 MEAN ABSORBANCE	10% E10MCR 90% E50LV MEAN ABSORBANCE	25% E10MCR 75% K100LV MEAN ABSORBANCE	10% E10MCR 90% K100LV MEAN ABSORBANCE
0	0.0000	0.0005	0.0000	0.0005
1	0.1095	0.1250	0.0790	0.1120
2	0.1855	0.1960	0.1360	0.1775
3	0.2570	0.2540	0.1845	0.2325
4	0.3220	0.3065	0.2300	0.2845
5	0.3870	0.3580	0.2715	0.3325
6	0.4505	0.4110	0.3125	0.3825
7	0.5140	0.4810	0.3525	0.4360
8	0.5780	0.5475	0.3905	0.4900
9	0.6220	0.5990	0.4305	0.5595
10	0.6645	0.6525	0.4730	0.6235
11	0.7020	0.6885	0.5210	0.6785
12	0.7255	0.7080	0.5685	0.7170
13	0.7395	0.7200	0.6045	0.7365
14	0.7510	0.7275	0.6415	0.7390
15	0.7560	0.7310	0.6715	0.7370
16	0.7600	0.7290	0.6905	0.7360
17	0.7630	0.7260	0.7080	0.7340
18	0.7650	0.7260	0.7225	0.7360
19	0.7670		0.7345	
20	0.7680		0.7395	
21	0.7700		0.7440	
22	0.7725		0.7450	
23	0.7740			
24	0.7755			

TABLE III

Release Profiles of Ibuprofen Lysine Using Various Ratios of K4M and a Low Viscosity HPMC				
Time [hr]	50% K4M 50% E5 MEAN ABSORBANCE	25% K4M 75% E15LV MEAN ABSORBANCE	25% K4M 75% E5 MEAN ABSORBANCE	25% K4M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1155	0.1010	0.0995	0.0815
2	0.1795	0.1700	0.1565	0.1390
3	0.2315	0.2335	0.2110	0.1895
4	0.2815	0.2905	0.2630	0.2365
5	0.3655	0.3490	0.3130	0.2815
6	0.4095	0.4360	0.4395	0.3260
7	0.4465	0.5510	0.5270	0.3705
8	0.4925	0.6430	0.5815	0.4225
9	0.5695	0.6990	0.6305	0.4850
10	0.6550	0.7405	0.6580	0.5435
11	0.7045	0.7560	0.6775	0.6000
12	0.7235	0.7565	0.6950	0.6500
13	0.7360	0.7515	0.7060	0.6740
14	0.7400	0.7445	0.7175	0.6920
15	0.7460	0.7415	0.7245	0.7040
16	0.7535	0.7450	0.7260	0.7220
17	0.7525	0.7435	0.7275	0.7315
18	0.7555	0.7415	0.7270	0.7380
19	0.7605	0.7405	0.7305	
20	0.7605	0.7400	0.7305	
21	0.7650	0.7425	0.7320	
22	0.7635		0.7310	
23	0.7660			
24				

TABLE IV

Release Profiles of Ibuprofen Lysine Using Various Ratios of K15M and a Low Viscosity HPMC				
Time [hr]	25% K15M 75% E5 MEAN ABSORBANCE	25% K15M 75% E15LV MEAN ABSORBANCE	25% K15M 75% E50 MEAN ABSORBANCE	25% K15M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1280	0.0935	0.0855	0.0950
2	0.2110	0.1540	0.1425	0.1640
3	0.2830	0.2085	0.1915	0.2225
4	0.3640	0.2590	0.2390	0.2740
5	0.4350	0.3070	0.2810	0.3215
6	0.5060	0.3530	0.3265	0.3665
7	0.6475	0.3980	0.3970	0.4120
8	0.7215	0.4470	0.4890	0.4575
9	0.7360	0.5505	0.5535	0.5040
10	0.7415	0.6200	0.5945	0.5485
11	0.7410	0.6655	0.6125	0.5910
12	0.7395	0.6815	0.6400	0.6245
13	0.7435	0.6850	0.6590	0.6490
14	0.7475	0.7040	0.6910	0.6650
15	0.7490	0.7250	0.7085	0.6845
16	0.7520	0.7365	0.7295	0.7035
17	0.7505	0.7395	0.7395	0.7160
18	0.7515	0.7390	0.7400	0.7235
19	0.7485	0.7405	0.7330	0.7305
20	0.7525	0.7405	0.7355	0.7345
21	0.7500	0.7360	0.7255	0.7385
22				0.7415

TABLE V

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC		
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
0	0.0000	0.0000
1	0.0820	0.1005
2	0.1330	0.1615
3	0.1800	0.2180
4	0.2225	0.2680
5	0.2630	0.3150
6	0.3025	0.3630
7	0.3405	0.4230
8	0.3805	0.4950
9	0.4240	0.5465
10	0.4880	0.5940
11	0.5510	0.6350
12	0.5945	0.6715
13	0.6335	0.7000
14	0.6650	0.7215
15	0.6950	0.7370
16	0.7195	0.7485
17	0.7395	0.7575
18	0.7530	0.7655
19	0.7680	0.7710
20	0.7740	0.7755
21	0.7795	0.7770
22	0.7825	0.7785
23		0.7800
24		0.7820

Claims

1. A carrier base material combined with ibuprofen or a salt thereof and shaped and compressed to a solid sustained release pharmaceutical dosage form having a zero order release profile upon administration in which the carrier base material consists essentially of (a) HPMC having a molecular weight of 60,000 or greater, and (b) HPMC having a molecular weight of 50,000 or less; and wherein the ratio of (a) to (b) is from 1:2 to 1:9.

2. A zero order release pharmaceutical formulation according to Claim 1 in which the high viscosity HPMC is selected from a methocel cellulose ether wherein:
   a) % methoxy = 19-24. % hydroxypropyl = 7-12, viscosity = 4000 cps;
   b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 10,000;
   c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4,000;
   d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 15,000;
   e) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100,000;
   and the low viscosity HPMC is selected from a methocel cellulose ether wherein:
   a) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4-6;
   b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 12-18;
   c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 40-60;
   d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100.

3. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part methocel cellulose ether wherein % methoxy = 28-30, % hydroxypropyl = 7-12 and viscosity = 10,000 and wherein the low viscosity HPMC is selected from:
   a) 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;

b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60; or
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

4. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
c) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

5. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

6. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is one part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 15,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

7. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60.

8. A zero order release pharmaceutical formulation according to Claim 2 wherein the medicament is selected from:
a) ibuprofen; or
b) salts of ibuprofen.

9. A formulation according to Claim 8 wherein the medicament is ibuprofen lysine.

10. A formulation according to Claim 9 wherein the medicament is (S)-ibuprofen-(S)-lysine.

11. A formulation according to Claim 10 wherein the amount of medicament as ibuprofen is 100 to 600 mg.

Patentansprüche

1. Trägergrundmaterial, kombiniert mit Ibuprofen oder einem Salz davon und geformt und komprimiert zu einer festen pharmazeutischen Dosierungsform mit langanhaltender Freisetzung mit einem Freisetzungsprofil nullter Ordnung bei der Verabreichung, worin das Trägergrundmaterial im wesentlichen besteht aus (a) HPMC eines Molekulargewichts von 60 000 oder mehr und (b) HPMC eines Molekulargewichts von 50 000 oder weniger und worin das Verhältnis von (a) zu (b) 1:2 bis 1:9 beträgt.

2. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 1, worin die hochviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:
a) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 4 000 cps,
b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 10 000,
c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4 000,
d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 15 000,

e) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100 000,

und worin das niederviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:

a) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4-6,
b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 12-18,
c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 40-60,
d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100.

3. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC zu einem Teil Methocel-Celluloseether ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 10 000 und worin das niederviskose HPMC ausgewählt ist aus:

a) 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,
b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,
c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60 oder
d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

4. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,
b) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,
c) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

5. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 Teil, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,
b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,
c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,
d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

6. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 15 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,
b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,
c) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,
d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

7. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,
b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60.

8. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin das Medikament ausgewählt ist aus:

a) Ibuprofen oder
b) Salzen von Ibuprofen.

9. Formulierung nach Anspruch 8, worin das Medikament Ibuprofen-Lysin ist.

10. Formulierung nach Anspruch 9, worin das Medikament (S)-Ibuprofen-(S)-Lysin ist

11. Formulierung nach Anspruch 9, worin die Menge des Medikaments als Ibuprofen 100 bis 600 mg beträgt.

Revendications

1. Matériau de base de véhicule associé à de l'ibuprofène ou un sel de celui-ci et façonné et comprimé en une forme pharmaceutique solide à libération prolongée, ayant un profil de courbe de libération d'ordre zéro après administration, caractérisé en ce que le matériau de base de véhicule consiste essentiellement en (a) une HPMC ayant une masse moléculaire de 60 000 ou plus et (b) une HPMC ayant une masse moléculaire de 50 000 ou moins; et en ce que le rapport de (a) à (b) va de 1:2 à 1:9.

2. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 1, dans laquelle la HPMC à haute viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 centipoises (cP);
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 10 000 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 15 000 cP;
   e) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 000 cP;
   et la HPMC à faible viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4-6 cP;
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 12-18 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 40-60 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 cP.

3. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'éther de cellulose de type Methocel dans lequel le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 10 000 cP, et dans lequel la HPMC à faible viscosité est choisie parmi:
   a) 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
   b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
   d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

4. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
   a) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   b) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

5. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:

a) 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

6. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 15 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

7. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP.

8. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle le médicament est choisi parmi:
a) l'ibuprofène et
b) des sels d'ibuprofène.

9. Composition selon la revendication 8, dans laquelle le médicament est l'ibuprofène lysine.

10. Composition selon la revendication 9, dans laquelle le médicament est le (S)-ibuprofène-(S)-lysine.

11. Composition selon la revendication 10, dans laquelle la quantité de médicament, en tant qu'ibuprofène, va de 100 à 600 mg.